Pulmonary Toxicity of Utah Valley PM: Are Empirical Indices of Adverse Health Effects Coherent with the Epidemiology?

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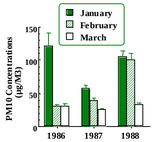
Science Question

Are empirical indices of adverse respiratory health effects coherent with epidemiologic reports on the pulmonary toxicity of Utah Valley PM?

- In 1989, Pope published a seminal article associating Utah Valley hospital respiratory admissions with PM_{10} levels from April 1985 - February 1988, a period inclusive of intervals of closure and operation of the Geneva Steel Mill. While operational, this plant contributed ≈ 82% of all industrial-related PM in the Utah Valley (47-80% of all sources). On August 1, 1986 the steel mill closed due to a labor strike and remained closed for one year until re-opening on September 1, 1987.
- Ambient PM_{10} measurements were made at a sampling sites downwind of the plant (e.g., in Lindon, Utah). PM concentrations were notably increased during winter months as temperature inversions trapped emissions in stagnant air near the valley floor.
- Pope observed that over 80% of monthly respiratory hospital admissions were significantly related to the mean as well as peak ambient PM_{10} levels for both the immediate and pre-vious months. These hospital admissions decreased soon after the plant closed and increased again when it re-opened a year later as did public complaints of respiratory discomfort. Other admissions and time periods did not exhibit any correlation nor did hospitals in areas not affected by Geneva show correlations with PM_{10}.
- The events of the closure and reopening of the steel mill in Utah Valley provided a unique opportunity by which morbidity among those in the affected area, in particular children with lung or airway impairment, could be correlated with ambient PM_{10} levels. (Pope CA, Am J Pub Health 1989; Pope CA, Arch Env Health 1991; Pope CA, Toxicology 1996).

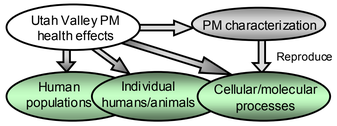
Based on data from the AIRS*Data* air pollution data base, monthly winter PM_{10} average concentrations at the Lindon, Utah monitoring site were lower during 1987.



Research Goals

- The overall goal of this research endeavor was to provide empirical toxicological data that would enhance the **biologic plausibility** of the purported **cause-and-effect** linkage between increased "plant-on" wintertime ambient PM levels in the Utah Valley and subsequent adverse respiratory health outcome.
- A multifaceted approach was used to address this goal.

Multifaceted Approach



Characterization of PM Extract Composition
Does the content of Utah Valley PM extracts from plant operational periods differ from that of its inactive period; and if so, what are these differences ?

Toxicology studies
In experimentally exposed humans and animals, is the relative pulmonary toxicity of PM extracts from plant operational periods greater than that of the inactive period ?

Cellular and molecular mechanistic studies
In directly exposed human- and animal-derived airway or phagocytic cells, is the relative toxicity of PM extracts from plant operational periods greater than that of the inactive period ?

Linking PM subcomponents to effects
Can any of these "adverse" effects be reproduced with known extract subcomponents; and if so, are these subcomponents likely related to emissions emanating from a fully functional steel mill ?

Methods

▪ **Filter acquisition.** Archived hi-vol filters collected at Utah Valley PM monitoring sites for winter months (Jan-March) of the year before plant closure (1986), during closure (1987), and the year after plant reopening (1988) were obtained from the Air Monitoring Center, Utah Division of Air Quality, Salt Lake City, Utah.

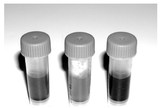
▪ **Filter extraction.** Equivalent numbers of filters from each of three consecutive winters were selected. PM subcompon-ents were extracted via agitation of filters in deionized water for 96 h. The liquid extracts were centrifuged to pellet relative-ly insoluble material. Supernatants from filters corresponding to the 1986, 1987 & 1988 winters were pooled / lyophilized.

▪ **Extract characterization.** Lyophilized extracts were characterized as to their recovered mass, general solubility, pH in suspension, endotoxin content, EC/OC content, oxidant generation potential, and elemental composition as determined by dissolution in 1.0 N HCl, using inductively coupled plasma-mass spectroscopy (ICP-MS) (EPA method 6020 analytical protocol) to evaluate 40 different elements.

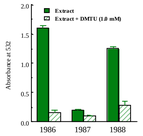
▪ **Toxicological approach.** Using equivalent masses of the extracted lyophilized material, the relative pulmonary toxicity of the 1986, 1987, and 1988 samples was established using an integrated toxicological approach. ***In vivo* studies** focused on development of lung/ airway injury, inflammation, and enhanced airway responsiveness in instilled laboratory **animals** and **humans**. ***In vitro* studies** utilizing pulmonary cell types from **animals** and **humans** were performed to discern direct cellular / molecular effects of extract exposure.

PM Characterization

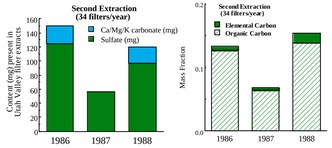
Extracts in suspension



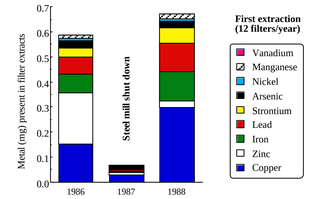
Oxidant Generation

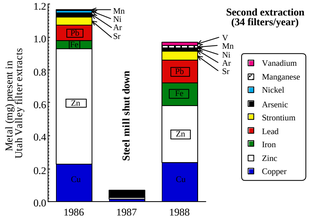


Sulfate, Cation, and Carbon Content



Metal Content

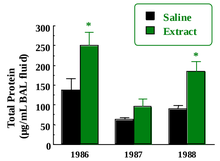




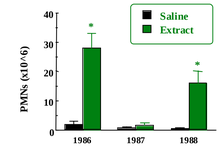
In Vivo Responses

Humans

Acute lung injury.

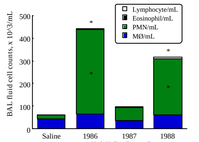


Neutrophilic lung inflammation.



Rodents

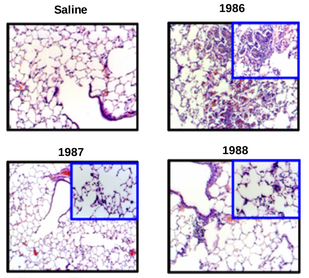
Neutrophilic lung inflammation.



Airway Responsiveness Testing (24 h)

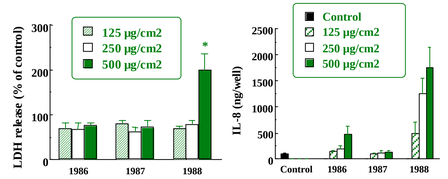
	Extract Exposure Saline	1986	1987	1988
ACh EC_{150} mean	6.0 ± 1.0	5.4 ± 1.0	6.9 ± 1.0	4.6 ± 0.8
Upper 95% CI	8.2			
Lower 95% CI	3.7			
% < lower 95% CI	17 % (2/12)	50 % (6/12)	25 % (3/12)	50 % (6/12)

Lung Pathology (24 h)

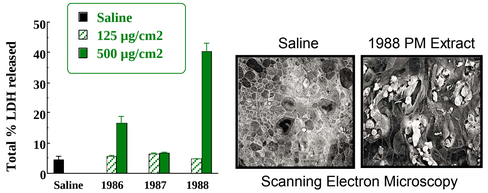


In Vitro Responses

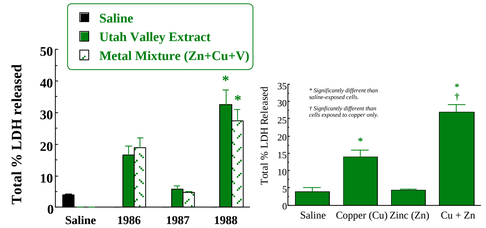
Human airway epithelial (BEAS-2B) cells



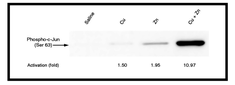
Rodent airway epithelial (RTE) cells



Metal mixture effects in RTE cells



▪ Co-exposure of primary airway epithelial cells to copper + zinc induced significantly greater stress and toxic responses than that observed during exposure to either metal individually.



Conclusions

- Coherent with the aforementioned epidemiological reports, on the whole these studies demonstrated that greater lung / airway injury and inflammation occurred after exposure to PM extracts from the steel mill operational periods relative to that of its inactive period.
- The ability to replicate the acute airway injury with represent-ative metal mixtures suggests that these metals are, to a large extent, mediating many of the acute airway effects observed. Metal interactions appear to play critical but complex roles in the overall effects observed.
- Moreover, if such "toxic" PM were to accumulate even in moderately high concentrations, as it seemingly did during the plant-operational wintertime temperature inversions, the combination (i.e., moderately high concentrations of relatively toxic PM) was directly associated with adverse respiratory health outcome for select individuals living in Utah Valley. Not surprisingly, individ-uals with underlying inflammatory airway disease appeared to be at greatest risk for disease exacerbation during these abrupt changes in ambient air quality.

Future Directions

One of the major limiting factors in using this sort of research approach to link PM ***source*** to **health outcome** is the limited availability of representative or "test" PM samples. Currently, multi-site collaborative studies are underway to collect significant ambient PM sample quantities at sites coincident with health study investigations to:

- Better devise empirical assessments of both PM components and related co-factors in an attempt to use detailed site-specific source apportionment models to ascertain source contributions to health effects caused by ambient PM
- Further evaluate the coherence between toxicological particle characteristics and epidemiological studies of air pollution health effects.

Impact and Outcomes

- The conceptual linkage between studies of human populations and empirical laboratory investigations validates further use of complementary human, animal, and cellular studies designed to define underlying mechanisms to further refine risk assessment paradigms and regulatory actions.
- It is also important to note that a multifaceted approach is essential to fully comprehend the various pathologic processes that may underlie PM's adverse health effects. Such information is critical to ensure that exposed populations, in particular susceptible individuals, are adequately protected by existing regulatory mandates.

Source to Health Outcome